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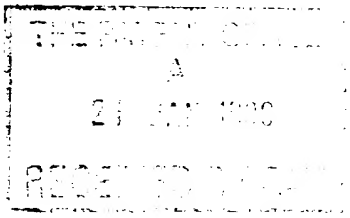

**The Patent Office**

Cardiff Road
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1. Your reference — PBA/D088328PGB

2. Patent application number *(The Patent Office will fill in this part)* — **9901272.6** — 21 JAN 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   ADVANCED MEDICAL SOLUTIONS LIMITED
   ROAD THREE
   WINSFORD INDUSTRIAL ESTATE
   WINSFORD
   CHESHIRE
   CW7 3PD
   UNITED KINGDOM

   Patents ADP number *(if you know it)* — 7587900001

   If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention — FIBRES

5. Name of your agent *(if you have one)* — Marks & Clerk

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   Sussex House
   83-85 Mosley Street
   Manchester
   M2 3LG

   Patents ADP number *(if you know it)* — 18004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day/month/year)* |
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day/month/year)* |
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8. Is a statement of Inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   *a) any applicant named in part 3 is not an inventor, or*
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| Priority documents | - |
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# FIBRES

## Field of Invention

The present invention relates to fibres and more particularly, but not exclusively, to fibres and materials comprised of such fibres for use in growing or culturing cells, e.g. for the purposes of tissue repair, in-vitro cell cultures and/or organ culture.

## Background

Medical devices that are implanted or used on broken skin in wound healing optimally require predictability in their interaction with surrounding tissues and blood. In some cases devices may act as templates for cell in-growth, in some cases they may have already been seeded with cells. Some devices require strong tissue in-growth for fixation, others may function best with minimal interaction. Understanding the biomaterial surface and the cell surface is clearly important in predicting what protein adsorption may occur and how cells may react in terms of adhesion, locomotion or active/passive response/transformation. The key determinants for the biomaterial surface will be surface chemistry in terms of hydrophobic/hydrophilic balance, surface charge, size and direction and counterion, physical size (macroscopic or microscopic), shape (geometry) and surface roughness/smoothness and mechanical properties (elasticity).

Substrates for tissue augmentation or to act as carriers for cultured cell transfer in wound therapy are usually collagen based. In this situation the collagen substrate usually has to be specific to the type of cell growth required and the phenotype and status (secretory, replicatory) grown on the substrate may not turn out to be as required.

It is the specific and non-specific physicochemical forces that will determine gene expression of the cell and phenotype the cell expresses will determine its status capability. It is known for example that cells grown on certain substrates will be

inhibited from undergoing terminal differentiation, this has been shown for keratinocytes by Adams & Watt. So the attraction of using non-collagen surfaces for artificial cell substrates is that the cells may retain a migratory and genotypic capability. The attachment to the cell whatever the substrate, collagen, vitronectin, thrombospondin will be through integrin cell-surface receptor.

Cells seeded onto the surface of a three dimensional structure may only grow in a two dimensional fashion or vice versa depending on the substrate. In some situations, for example nerve regeneration, it is desirable for there also to be not only be predictability of attachment and growth but also direction. In the case of nerve regeneration this would mean that an axon could be directed to grow back down its original sheath. Similarly it may be desirable that a cell grow not only on particular direction, but that a group of cells may grow in the same direction. In the case of voluntary muscle, the muscle belly is made up of muscle cells orientated with their long axes in parallel. Organs such as blood vessels rely on layers of muscle fibres with different layers orientated in a direction at 90° to the previous layer.

Historically work on guiding cells has shown that cells can be directed to migrate along the direction of surface deformations (scratches). Carter et alia (Hapto laxis), can be orientated by fluid shear (Eskin et alia, Ives et alia) by axial strain (Ives et alia). Others have shown that orientation of the Fn molecule can direct cell growth.

US patent 5,610,148 (Robert Brown) entitled "Macroscopically Orientated Cell Adhesion Protein" describes the production of a fibre comprised of fibrils of the cell adhesion protein fibronectin (Fn) that has been denatured and the polymer chains then aligned by unidirectional shear allowing aggregation and precipitation. Cells seeded onto these fibres demonstrate directional cell growth as a result of the longitudinal orientation of the cell adhesion-binding site.

**Summary of Invention**

According to the present invention there are provided fibres having an open-topped channel formation extending along the length of the fibre and being capable of providing guided cell growth along the length of the channel.

The fibres may be used to form a range of structures for use in providing cell growth, as described more fully below.

The fibre structures predict cell adhesion, migration, direction and orientation. In the preferred embodiments, microfibrous scaffolds are disclosed that are composed of fibres designed to support cell attachment and directed cell motility and cell growth. The advantage of these fibres is they can be tailored to drive specific cell and tissue performance features by varying the level of cell adhesion protein, surface charge, counterion presence or absence of growth factor, as well as their geometry, fibre orientation and axial strain; various embodiments of the fibres can be envisaged matrices, bundles, tubes, etc. The advantage of matrices made from these fibres is that the fibres can be random or have varying levels of orientation, layers of different types of fibre designed to suit different cell types can also be used. The fibres may also be mixed biodegradable and stable and vary in density and be shaped to form a template such that some mechanical, functional loading could be predicted that as degradation occurred would be counter balanced by appropriate tissue in growth, the advantages of these structures over collagen based substrates is that the seed cells once adhered will secrete and lay down there own extra-cellular matrix. Embodiments of the fibres with cell tracks or cell troughs that ensure that cells positioned at one end of the fibre will deliver to a point along the same fibre may be used in nerve regeneration where the damaged axon needs to grow back to its previous terminus are described. Besides non-woven matrices, embodiments may be knitted or woven structures that produce sheets or tubes useful in tissue repair or replacement, e.g. dermal substitute, vascular graft. Embodiments utilising the orientational/directional nature of the cell growth on these fibres and fibre scaffolds

may be in vitro growth of muscle where muscle cell growth may be unidirectional along parallel fibre.

It is particularly preferred that the fibres are of alginate material which for preference incorporates a cell adhesion protein most preferably fibronectin, vitronectin, or con Willebrand protein. The cell adhesion protein may be provided solely within the channel.

Fibres in accordance with the invention may be produced by spinning solution of the material of which the fibre is to be formed through an orifice into a coagulation bath. The orifice may be configured such that the fibre solidifies into a form incorporating a channel. Alternatively the orifice may be associated with an engraving device so that the channel is "cut" into the fibre as it is formed. In either case, the coagulation bath may incorporate a material, e.g. a cell adhesion protein, to be adsorbed/absorbed into or onto the fibre surface.

**Description of Preferred Embodiments**

The fibres may be, but are not necessarily, of circular cross-section. The channel may extend generally linearly parallel to the axis of the fibre but other channel configurations which extend along the fibre length are also possible, e.g. helical. The channel may extend along the full length of the fibre or terminate short of one or both ends thereof. The fibres may have two or more channel extending, for example, generally in parallel to each other.

The fibres may have a length of 1mm to 1000mm (more preferably 5mm-500mm) and preferably a diameter of 10μm-100μm.

It is preferred that the channel has a depth which is not more than 2/3 the diameter (or maximum cross-sectional dimension) of the fibre but not less than the width of an unspread cell (generally considered to 10μm -20μm. The width of the channel is preferably no greater than half the radius.

In certain embodiments of the fibre, the depth of the channel may be less than the width thereof. In other embodiments the channel depth may be greater than or equal to the width of the channel.

Preferred embodiments of fibre in accordance with the invention have a channel whereof the width and depth are each at least 20μm.

The channel in the fibres may be of any desired configuration, e.g. U, "rectangular" or "square"-U, or V-shaped.

Examples of preferred dimension for a 30μm fibre are shown in the following tables:

**Fibre + Groove**

| Width/Depth | Ideal range of 30μm fibre | Maximum groove size in relation to the fibre dimension | Minimum groove size in relation to cell dimension |
|---|---|---|---|
| Width | 5-20μ | 1/20 fibre circumference | 1/20 cell circumference |
| Depth | 3-10μ | 1/10 fibre diameter | N/A |

**Fibre + Trough**

| Ideal range of 30μm fibre | Ideal range of 30μm fibre | Maximum trough size in relation to fibre dimension | Minimum trough size in relation to cell dimension |
|---|---|---|---|
| Profile | V.U | | |
| Width | Normally 5-30μ | Fibre diameter < | 1 x cell diameter |
| Depth | Normally 5-30μ | Radius ≤ | 1 x cell diameter |

The above preferred dimensions may be readily adapted for fibre widths other then 30μm.

The fibre preferably comprises a biodegradable biopolymer or a combination of such polymer, examples of which include alginic acid salts (e.g. calcium alginate, carboxymethylcellulose, Methoxypectin, chitosan, chitosan derivatives (e.g. chitosan glutammate), and hyaluronic acid.

The channel of the fibre may have a coating of the protein, for example a blood plasma protein (e.g. fibronectin/fibrinogen), cascin, albumin or gelatine.

The fibres may be formed into a structure, e.g. random matrices (e.g. non-woven felts and fleeces), orientated matrices (fibres having some relative alignment), knitted structure (e.g. knitted cloths), braided structures (e.g. braided thread), bundled structures, and carded silver.

Following the principles outlined above a range of devices may be constructed from the fibres that are designed to allow cell attachment and growth (although it may be cell type specific) but is unique in that the fibre structure will cause the cell to grow down the fibre and thus be delivered to any point along, or at the other end of the fibre, for which we use the term "guide wire cell growth". The fibre structure that

is unique in being able to predict this cell response is one where the bulk fibre maybe made of calcium alginate or other materials as described for different embodiments that has been formed with a groove along its length (Figure 1). The size of the fibre groove would normally about 1/20 of the unspread circumference of the cell, the size of the groove would normally be the diameter of an unstuck cell depending on the cell type but large enough to allow the cell to adhere and spread whilst retained within the groove. It is possible that the cell profile may stay entirely within the groove and not be above the circumferential profile of the fibre. In the past various inventions have been proposed or actually utilised hollow fibre structures to grow cells and overcome some of the problems of growth on the surface of the fibre alone. The current grooved fibre structure proposed gives the benefits of both a fibre and hollow fibre in that the cells are in direct contact with the media whilst on a fixed and potentially permeable substrate but the level of surface fluid shear or mechanical shear to which the cell is exposed. If cells are placed on the inside of a hollow fibre allowing the cell to feed only by diffusion through the fibre wall there may be problems because of molecular weight cut off and tendency for the lumen of the main fibre to get blocked by cell growth reducing diffusion capability. In this circumstance the indent may be deep enough to describe as a trough. Depending on the size of the groove relative to the cell, the cell will tend to move along it.

The groove will produce a concentration of surface charge and energy and hence affect the nature of the protein adsorption but in the case of fibronectin will ensure a concentration at and in the groove and if absorbed on the appropriate surface or with an appropriate second protein the fibronectin will expose its cell adhesion binding site (Grinnell et alia).

It has also been shown in prior studies by Carter et al that cells seeded into a flat surface which have been scratched will align (Haptotoxis) and move along the track of the scratch (Figure 2) and their motility will be greater than that on the flat surface. The fibre can be co-extruded so that as the bulk fibre is produced the groove has a protein solution ejected preferentially into its centre; it may also be preferable to surface absorb a non-cell adhesion active protein to the rest of the fibre. The

advantages to using an adhesion substrate other than collagen is that the cells once adhered and growing will lay down their own basement membrane and extra cellular matrix proteins, this eliminates the need for collagen specificity and the problems therein. Using synthetic substrates of the right chemistry it is also possible for the status of the cell and its phenotypic versus geotypic expression to be controlled.

By controlling the chemistry of the counterion of the fibre various cell types may preferentially adsorb or be encouraged to move faster or spread/adhere more or tightly to the fibre. Using this fibre structure cells can be guided down into three-dimensional matrices or can be encouraged to arrive at a specific location. Cells of different types can be seeded to grow into different parts of the structure. Cells are thus oriented on the fibre but by orienting the fibre itself all the cells in a structure maybe oriented. Chemotactic/migratory gradients may also be set up along the length of the fibre in order to speed up response.

It has also been shown by Ives et al that cells that are subjected to axial stress will align across the direction of stress so in an embodiment where cells are grown on an elastic fibre (Figure 3) and have been allowed to grow into and between fibres to a point where a three cell structure has been formed by applying axial stress to the fibres the cells will be encouraged to align across the fibres to minimise the exposure. Using this technique for instance a structure seeded with muscle fibres could be organised so that the muscle cell contraction will produce a directional contraction and shortening. In some circumstances it may be appropriate to seed cells onto the fibres in a proteinaceous media in another single or multi protein solution depending upon the activity required. Similarly the fibre may be made of a biodegradable material e.g. biopolymers such as alginate or chitosan gelatin guar gum, etc. or synthetic polymers such as polylactic, polyglycolic or a non-degradable such as polyurethane, etc.

**Wound Therapy**

In an embodiment for wound therapy a bundle of fibres with troughs may be seeded with keratinocytes allowed to grow whilst suspended in culture media and then fibres laid singly in parallel across the wound. Cells in the trough being protected from the shear and damage of culture and handling and readily laying down a new basement membrane when placed on the wound.

**Bioreactors**

In an embodiment for bioreactors, the use of fibres with troughs provides a structure that would provide the ideal mammalian cell bioreactor. Cells can remain below the circumferential profile of the fibre and thus still be exposed to the culture media for diffusion of nutrients but no to the surface shear. For some cell types and with the appropriate substrate it may be possible to use axial stress to stimulate, align disrupt or detach cells depending on the amount of stretch.

**Nerve Guidance**

In an embodiment for nerve guidance the fibres would be structured with a trough the size appropriate to the axon and bundles of fibres oriented in parallel with the end of the fibre being in the same position at both proximal and distal positions. Fixation of bundle so that the ends were in apposition to the two ends of the cut nerve would allow directional and positional regeneration of the nerve.

**Vascular Grafts**

Grooved fibres would be formed into a tube by either winding onto a mandrel or knitting. By combing trough fibres with groove fibres cell alignment can be controlled by both fibres direction and axial stress so the desired layers of orientation could be obtained.

**Methods to obtain the groove or trough on the fibre.**

The groove or trough is made on fibres produced by a wet spinning process comprising the following steps:

Extrusion, precipitation, stretching, washing, drying.

(1) The groove or trough is generated by extrusion of the solution through an orifice or a spinneret with a multitude of holes. The orifices have round shape with 1 or more grooves/troughs or a combination thereof. The grooves have preferably dimension of cell (width 5-10μm) or multiple thereof.

(2) The groove or trough may be produced by engraving the fibre with a sharp blade or engraver. Alternatively the incision can be made by passing the fibre through a rough surface. The roughness is given to the surface by micro-prominences (peaks convexities) having the shape of the groove/trough. They are positioned as the appropriate distance to engrave various fibres. The incision may be made at different stages of the production process of the fibres: after the filament precipitation, after stretching, after the washing, after the drying. It is advisable to groove the fibre after the filament has precipitated out in a short coagulation bath. It will subsequently re-coagulate in its engraved structure in another bath.

(3) The groove/trough can be obtained by etching (1.M)

**Ideal profile of the groove/trough**

A variety of configuration of fibres configurations can be produced with single or multi-grooves with parallel, spiralled or transverse grooves could be envisaged.

**How to absorb protein onto the surface of the fibres**

(1) Extrusion of the bulk filament in a bath containing the protein that will coat it. The precipitation of the fibre occurs thanks to the protein that provides the counterions for the chemical bound.

(1a) Extrusion through a co-axial nozzle where the proteinacious component is ejected from the external cylinder and the bulk solution form the internal one.

(2) Precipitation of the bulk filament in a coagulation bath and consequent coating with the protein solution in a second bath.

(3) Impregnation with proteinacious solution of 2 or more fibres bundled together to generate angles or interstices. The bundles can be obtained by converging to one or more filaments just after the extrusion in the coagulation bath or using an additive (e.g. polyoxyethylene sorbitan monolaurate, *Tween 20*) that promotes adherence of the fibres, in the washing bath. An angular surface can also be generated by twisting or braiding 2 or more fibres.

**Chemical composition of the fibres**

Bulk filament is made preferably of biodegradable biopolymer or combination thereof.

These are preferably:

Salt of alginic acid (e.g. calcium alginate)

Carboxymethylcellulose

Methoxypectin

Chitosan

Chitosan derivatives (e.g. chitosan glutammate)

Hyaluronic acid

The coating is made preferably of protein:

Blood plasma proteins (e.g. fibronectin/fibrogen)

Cascin

Albumin

Gelatine

Etc.

**Fibre can be processed using textile technologies into the following formats:**

Non woven fleece

Carded Silver
Knitted cloth
Braided thread.

**Process for making grooved or troughed fibres with an adsorbed protein coat**

The fibres for use in the microfibrous scaffolds described may be made by a variety of routes:-

1. Two stage with fibre precipitation/formulation and then surface adsorption/secondary precipitation of protein of synthetic polypeptide using consecutive baths.

2. Single stage fibre formulation and adsorption.

3. Three stage with fibre formulation followed by fibre engraving followed by surface adsorption.

4. Combinations of the above.

5. Electrostatic spinning.

6. Solvent evaporation.

7. Melt extruded.

8. Etching.

The key principle behind the process is the use (in the preferred embodiment of the invention) of calcium alginate to drive the precipitation and formulation of a fibre. Using the ejection of a solution from a nozzle or spinneret with a multitude of

nozzles that have a defined shape (round, round with grooves and round with a trough).

The chemistry of the solution can be of a biodegradable synthetic or biopolymer or non-degradable polymer. The shape of the fibre can be defined at the point of precipitation or by an engraving step after precipitation. In a similar fashion protein may be deposited in to the groove or trough of the fibre either at the point of fibre formulation or later. A variety of fibre configurations with single or multi-grooves with parallel, spiralled or transverse grooves could be envisaged.

Fibres can be fabricated into other structures by various textile techniques that may produce the following type by:

1. Random matrices (non-woven felts)
2. Orientated matrices (fibres have some relative alignment)
3. Knitted
4. Woven.
5. Braided
6. Bundled
7. Fusion.

## CLAIMS

1. Fibres having an open-topped channel formation extending along the length of the fibre and being capable of providing guided cell growth along the length of the channel.

2. Fibres as claimed in claim 1 having a length of 5mm-500mm.

3. Fibres as claimed in claim 1 having a diameter of 10μm-100μm.

4. Fibres as claimed in claim 1 wherein the depth which is not more than 2/3 the diameter (or maximum cross-sectional dimension) of the fibre but not less than 10μm.

5. A fibre as claimed in any one of claims 1 to 4 wherein the width of the channel is no greater then half the radius of the fibre.

6. Fibres as claimed in any one of claims 1 to 5 wherein a cell adhesion protein is provided in the channel.

7. Fibres as claimed in claim 6 wherein the cell adhesion protein is preferentially located in the channel.

8. Fibres as claimed in claim 7 wherein the cell adhesion protein is fibronectin.

9. Structures comprised of fibres as claimed in any one of claims 1 to 8.

10. A fibre with a groove; the depth of the groove normally no more than 2/3 the diameter of the fibre but at least the width of an unspread cell (normally 10-20μ) and width no greater than ½ the radius.

11. A fibre as claimed in claim 10 with Fn preferentially adsorbed into the groove.

12. A fibre as claimed in claims 10 or 11 that allows for cell adhesion and guided migration and growth.

13. A fibre with a trough where the trough is at least 20 microns wide and 20 microns deep.

14. A fibre as claimed in claim 13 with Fn, preferentially adsorbed in the trough or in a groove in a trough.

15. A random microfibrous cell scaffold composition for growing cells to produce functional tissue replacements "in vivo".

16. A fibre as claimed in claim 14 in which various levels and types of growth factor have been entrapped allowing diffusion to the surface to control growth.

17. A scaffold as claimed in claim 15 in which fibres are oriented.

18. A scaffold as claimed in claim 15 in which fibres of different composition are layered.

19. Fibres as claimed in claim 14 aligned in parallel on a permeable flat surface (i.e. a semipermeable film) and seeded with cells.

20. Fibres as claimed in claim 14 used as cell culture substrates for use in bioreactors also for freezing and thawing cells.

21. A fibre as claimed in claim 10 or 11 that allows axial stress to be applied to the cell.

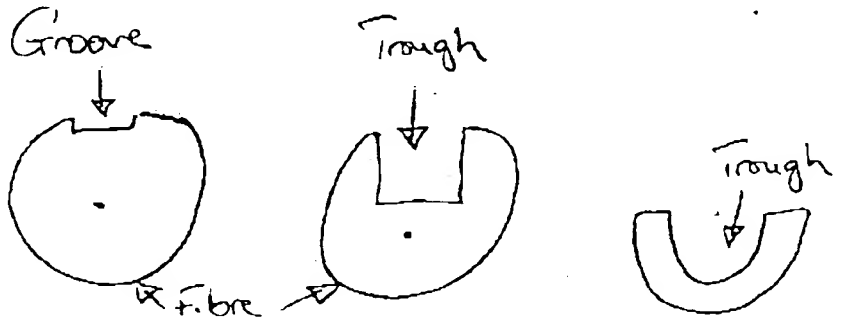
22. A fibre as claimed in claim 13 where the profile of the trough is U, "square" or "rectangular-U or V-shaped.

23. A fibre as claimed in claim 13 where there are multiple troughs around the circumference of the fibre.

24. A fibre composed of fused fibres, as claimed in claim 10 or 13 where either all of the same size or with a large central fibre with smaller fibres fused along its length.

## ABSTRACT

The fibre structures predict cell adhesion, migration, direction and orientation. In the preferred embodiments, microfibrous scaffolds are disclosed that are composed of fibres designed to support cell attachment and directed cell motility and cell growth. The advantage of these fibres is they can be tailored to drive specific cell and tissue performance features by varying the level of cell adhesion protein, surface charge, counterion presence or absence of growth factor, as well as their geometry, fibre orientation and axial strain; various embodiments of the fibres can be envisaged matrices, bundles, tubes, etc. The advantage of matrices made from these fibres is that the fibres can be random or have varying levels of orientation, layers of different types of fibre designed to suit different cell types can also be used. The fibres may also be mixed biodegradable and stable and vary in density and be shaped to form a template such that some mechanical, functional loading could be predicted that as degradation occurred would be counter balanced by appropriate tissue in growth, the advantages of these structures over collagen based substrates is that the seed cells once adhered will secrete and lay down there own extra-cellular matrix. Embodiments of the fibres with sell tracks or cell troughs that ensure that cells positioned at one end of the fibre will deliver to a point along the same fibre may be used in nerve regeneration where the damaged axon needs to grow back to its previous terminus are described. Besides non-woven matrices, embodiments may be knitted or woven structures that produce sheets or tubes useful in tissue repair or replacement, e.g. dermal substitute, vascular graft. Embodiments utilising the orientational/directional nature of the cell growth on these fibres and fibre scaffolds may be in vitro growth of muscle where muscle cell growth may be unidirectional along parallel fibre.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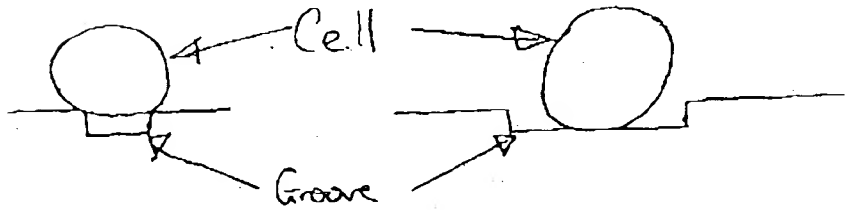
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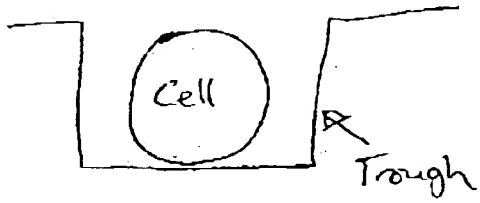
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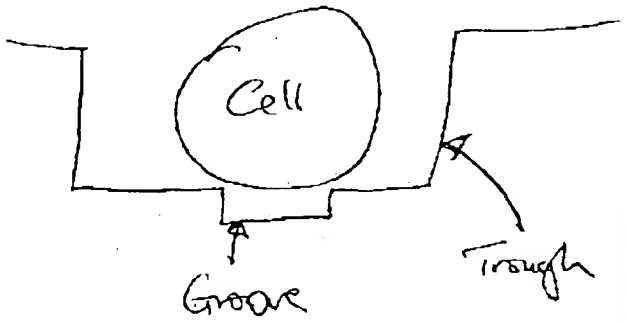
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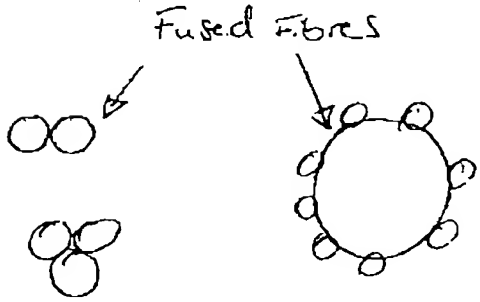
Fused Fibres